Pharmacy Update
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In This Issue

Aromatase Inhibitors for Breast Cancer

Anastrozole (Arimidex®) and Letrozole (Femara®)

Breast cancer is the most frequently diagnosed malignancy and the second most common cause of cancer-related deaths in women. Hormonal therapies that inhibit estrogen action or production have been used successfully for various stages of breast cancer. Tamoxifen is the most widely used hormonal manipulation and has been shown to prolong survival when given as adjuvant therapy or in combination with chemotherapy. When patients fail tamoxifen therapy, a second hormonal manipulation may be considered. Traditionally, progestins (i.e., megestrol, medroxyprogesterone acetate) or aminoglutethimide have been used. Approximately 30% of patients respond to megestrol therapy. Aminoglutethimide, a nonspecific aromatase inhibitor, produces response rates ranging from 28% to 43%. It may also significantly inhibit desmolase complex enzymes which are responsible for the initial step in the production of adrenal steroids. Therefore, hydrocortisone and fludrocortisone supplementation is sometimes necessary in patients receiving aminoglutethimide.

The aromatase inhibitors, anastrozole and letrozole, were developed to be more specific and potent than aminoglutethimide. Anastrozole (Arimidex®) and letrozole (Femera®) are indicated for the treatment of advanced breast cancer in postmenopausal women who have disease progression following previous antiestrogen therapy.

Pharmacology

Anastrozole and letrozole are highly potent and selective nonsteroidal aromatase enzyme complex inhibitors. Aromatase is responsible for the peripheral conversion of androgens to estrogens. In postmenopausal women, the majority of estrogen production comes from aromatization of adrenal androgens to estrone or estradiol. Anastrozole reduces estradiol serum concentrations to 70%-80% of baseline values within 24 hours. These effects are dose-dependent and persist for approximately 6 days after the drug is discontinued. Anastrozole has no effect on other circulating adrenal steroids (e.g., cortisol, androstenedione, dehydroepiandrosterone). Similar reductions in estrone or estradiol concentrations, with no changes in other hormones, are seen following letrozole administration.

Pharmacokinetics

Anastrozole is rapidly absorbed from the gastrointestinal tract, and peak plasma concentrations are obtained within two hours of oral administration. Administration with food decreases the rate, but not the extent, of absorption. The elimination half-life is 30 to 60 hours with no differences reported between female volunteers and female breast cancer patients. Anastrozole is extensively metabolized by the liver (≈ 85%), and only 10% of the drug is excreted unchanged in the urine. Letrozole is also rapidly absorbed following oral administration and is extensively metabolized by the cytochrome P450 3A4 and 2A6 isoenzymes. The elimination half-life of letrozole is approximately two days, and 6% of the drug is excreted unchanged in the urine. Advanced age does not appear to affect the pharmacokinetics of letrozole, and steady-state concentrations are not significantly affected by changes in renal function. The area under the plasma-concentration-time curve (AUC) is increased in patients with hepatic dysfunction,

but remains within the range seen in patients without liver dysfunction. It is not known if severe liver disease affects the pharmacokinetics of letrozole.

Selected Clinical Studies

Two randomized, single-blinded trials have compared 1 mg and 10 mg of anastrozole daily to 160 mg of megestrol daily in postmenopausal breast cancer patients who failed or whose disease progressed after initial hormonal therapy (Table 1). In both trials, the major clinical endpoints at 6 months were time to disease progression, time to treatment failure, and time to death. In these trials, the objective response rates were not different between treatment groups. Quality-of-life scores were better in the physical domain for anastrozole 1 mg daily and better in the psychological domain for anastrozole 10 mg daily when compared to megestrol ($p < 0.025$ for both). In a follow-up analysis at 31 months, patients treated with anastrozole 1 mg daily had a significantly prolonged overall survival (hazard ratio 0.78, $p = 0.02$) and a longer two-year survival (56.1%) compared to megestrol (46.3%).

Two randomized, single-blinded studies have compared letrozole 0.5 mg or 2.5 mg daily to either megestrol or aminoglutethimide in postmenopausal women who failed or whose disease progressed after initial hormonal manipulation (Table 1). At the 35-month follow-up period, patients who received letrozole 2.5 mg daily had a significantly improved objective response rate, a longer response duration, and a longer time to treatment failure compared to megestrol. In addition, 2.5 mg of letrozole was superior to 0.5 mg of the drug in terms of objective response rate, time to treatment failure, and time to disease progression. When compared to aminoglutethimide, the relative risk of disease progression was significantly lower with letrozole 2.5 mg daily. The time to disease progression, time to treatment failure, and duration of clinical benefit were significantly longer with letrozole 2.5 mg daily when compared to either letrozole 0.5 mg daily or aminoglutethimide at the 33-month follow-up period. Letrozole 2.5 mg daily, but not 0.5 mg daily, was associated with significantly prolonged survival when compared to aminoglutethimide (RR 0.68, $p = 0.02$). There are no published studies directly comparing anastrozole to letrozole.

Adverse Effects

Both anastrozole and letrozole are well tolerated. The principal adverse effects associated with anastrozole are asthenia, headache, nausea, hot flushes, and pain. Nausea and vomiting are more common with the 10-mg dose than the 1-mg dose. The nausea is generally mild and improves with continued therapy. Compared to megestrol, anastrozole is associated with more gastrointestinal disturbances, but weight gain, peripheral edema, and dyspnea are less frequent. The most common adverse effects associated with letrozole include nausea, musculoskeletal pain, headache, peripheral edema, hot flushes, and fatigue. Compared to megestrol, letrozole is associated with fewer adverse cardiovascular events, less weight gain, fewer thromboembolic events, and less vaginal bleeding.

Drug Interactions

In vitro, anastrozole inhibits cytochrome P450 1A2, 2C8, 2C9, and 3A4 isoenzymes. Anastrozole does not inhibit enzymes that metabolize dextromethorphan or coumarins. Concentrations that are 30 times higher than those expected from a daily 1-mg dose can cause 50% inhibition of enzymes that metabolize nifedipine, tolbutamide, and phenacetin. Letrozole is a potent inhibitor of cytochrome P450 2A6 and a moderate inhibitor of cytochrome P450 2C19. Letrozole does not appear to interact signifigantly with either cimetidine or warfarin.

Contraindications and Precautions

Both anastrozole and letrozole are teratogenic, embryotoxic, and fetotoxic and are classified as FDA pregnancy Category D. There are no controlled studies using either drug in pregnant women. Pregnancy should be ruled out in patients before initiating anastrozole or letrozole therapy. Letrozole has been associated with decreases in lymphocyte counts, and periodic monitoring of complete blood counts should be considered. Both anastrozole and letrozole have been associated with elevations in some liver function tests in patients with and without liver metastases. For this reason, periodic monitoring of liver function should be considered. Despite decreased clearance in elderly patients and those with mild to moderate hepatic disease, no dose modifications for anastrozole or letrozole are suggested at this time. For patients with renal impairment, dosage modifications are not necessary for those with creatinine clearances greater than 10 mL/min.

Dosage and Administration

The recommended dose of anastrozole for advanced breast cancer in postmenopausal women is 1 mg once daily. For letrozole, the recommended dose is 2.5 mg once daily. Patients treated with either anastrozole or letrozole do not require glucocorticoid or mineralocorticoid replacement therapy.

Medication	Dose	Daily Cost*
Aminoglutethimide	500 mg daily	$1.33
Megestrol acetate	160 mg daily	$1.46
Anastrozole	1 mg daily	$5.27
Letrozole	2.5 mg daily	$3.90

**Based on Federal Supply Schedule*

Conclusion

Oral therapy with either anastrozole or letrozole results in an equivalent or improved response rate when compared to standard secondary therapy (megestrol or aminoglutethimide) for postmenopausal women with progressive breast cancer. Although there are no direct comparative studies, anastrozole and letrozole appear to be therapeutically equivalent. Both medications are well tolerated and appear to have fewer adverse effects than either megestrol or aminoglutethimide. Ongoing studies will determine whether these agents have a role as initial hormonal therapy in patients with breast cancer.

References available upon request.

Table 1. Randomized Trials Comparing Aromatase Inhibitors to Other Second-line Hormonal Interventions for Advanced Breast Cancer

	Anastrozole						Letrozole					
	Jonat et al			Budzar et al			Dombernowsky et al			Package insert and Marty et al		
	Anastrozole		Megestrol	Anastrozole		Megestrol	Letrozole		Megestrol	Letrozole		Aminoglutethimide*
	1 mg daily	10mg daily	160mg daily	1 mg daily	10mg daily	160mg daily	0.5 mg daily	2.5 mg daily	160 mg daily	0.5 mg daily	2.5 mg daily	500 mg daily
Sample size (n)	135	118	125	128	130	128	188	174	189	193	185	179
Response (%) (CR+PR+SD)	34.1	33.9	32.8	37	30	36	27.2	34.5	31.7	33	36	30
Response (%) (CR + PR)	10.4	12.7	10.4	10	6	6	12.8	23.6‡ (p=0.04)	16.4			
CR (%)	1.5	2.5	2.4	3	1	2	3.2	6.9	4.2			
PR (%)	8.9	10.2	8	7	5	4	9.6	16.7	12.2			
SD (%)	23.7	21.2	22.4	27	24	30	14.4	10.9	15.3			
Progression (%)	58.5	50.8	56	48	50	52						
Survival (%)	84.4	81.4	77.6									
Time to Treatment Failure (days)	121	128	115				96	153‡ (p=0.002)	117			
Median Time to Progression (days)	132	156	120	170	143	151				103	123	112
Duration of Response (days)	261	†	257	168	133	125	546	†‡ (p=0.02)	537	619	706	450
Duration of Clinical Benefit (days)							543	705	435	525	696§	369
Time to Death (days)							654	770	655	636	792	592

CR = Complete response
PR = Partial response
SD = Stable disease ≥ 6 months
* Plus hydrocortisone
† Endpoint had not yet been reached at time of analysis
‡ Significant difference when compared to megestrol
§ Significant difference when compared to aminoglutethimide

Did You Know . . .

- Sildenafil (Viagra®), an oral phosphodiesterase-5 antagonist for the treatment of male impotence, should not be taken concurrently with organic nitrates. This is due to the potential for large and sudden drops in systemic blood pressure when these agents are combined.
- A recent study published in the *New England Journal of Medicine* reported that Type 2 diabetics experience improved glycemic control when metformin and troglitazone are used in combination.
- The tablet formulation of desmopressin (DDAVP®) is now approved for the treatment of childhood nocturnal enuresis.
- Graftskin (Apligraf™), recently approved for the treatment of venous leg ulcers, is the first bilayered skin product composed of living human cells.
- The FDA Antiviral Drugs Advisory Committee has recommended that rifapentine (Priftin®) receive accelerated approval for the treatment of pulmonary tuberculosis.
- SP-303 (Provir™), a new medication currently in Phase III clinical trials for the treatment of diarrhea in patients with AIDS, has been granted a Fast Track Product designation by the FDA.

Formulary Update

The Pharmacy and Therapeutics Committee has recently approved the following formulary actions:

Additions:

- Zolpidem (Ambien®), a benzodiazepine for the short-term management of insomnia
- Anastrazole (Arimidex®), an oral aromatase inhibitor for the treatment of advanced breast cancer in postmenopausal women
- Nicotine transdermal system (Nicoderm CQ®), for smoking cessation

Deletions:

- Flurazepam (Dalmane®)

Editors' Note

We wish to thank Barry Goldspiel, Pharm.D., F.A.S.H.P., for his contributions to this issue of *Pharmacy Update*.

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